REACTIONS OF 1,5-DIKETONES.

42.* SYNTHESIS OF HETEROCYCLES BY THE REACTION OF 4,4-DIMETHYL-1-PHENYL-1-(2'-OXOCYCLOALKYL)-3-PENTANONES WITH NITROGEN-CONTAINING NUCLEOPHILES

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The reaction of 1,5-diketones containing a pivaloyl fragment with several nitrogen-containing nucleophiles was studied. Derivatives of 2-tert-butyl-1,4-dihydropyridine were obtained and the direction of heterocyclization upon the reaction of these diketones with primary amines containing an additional nucleophilic site was elucidated. The facile free-radical cleavage of the angular tert-butyl group was demonstrated.

The results of the reaction of 1,5-diketones with nitrogen-containing nucleophiles depend to a considerable extent on the structure of the 1,5-diketones studied. In some cases, this reaction does not proceed at all [1]. The reaction of 1,5-diketones with amines containing an additional nucleophilic site leads to the formation of hydrogenated azolo- and azinopyridines [3], although the regioselectivity for unsymmetrical diketones has hardly been studied and the effect of the nature of the nucleophile on regioselectivity has not been clarified. The properties of the products also depend significantly on the nature of the starting 1,5-diketone [3].

Thus, we examined the action of such nucleophiles on 1,5-diketones containing a tert-butyl group next to the carbonyl group, namely, 4,4-dimethyl-1-phenyl-1-(2'-oxocycloalkyl)-3-pentanones (Ia and Ib) [4].

The mass spectra of diketones Ia and Ib contain ion fragments with m/z = (M − 57) which correspond to the loss of a tert-butyl group from the molecular ion and with m/z = (M − 84) for Ia and m/z = (M − 98) for Ib, which corresponds to loss of cyclopentanones and cyclohexanone, respectively, from the molecular ions. The fragmentation of the molecular ions by retro-Michael cleavage is characteristic for the mass spectra of 1,5-diketones [5].

The IR bands for the carbonyl groups in diketone Ia are found at 1700 and 1740 cm^{-1} and correspond to the pivaloyl and cyclopentanone carbonyls, respectively. Both the CO groups in Ib give a band which appears at 1700 cm^{-1}.

Diketones Ia and Ib form monoximes at the acyclic carbonyl. The band at 1740 cm^{-1} is absent in the spectrum of the monoxime of diketone Ia. The band at 1700 cm^{-1} is retained in the spectra of both monoximes and a low-intensity band at 1660 cm^{-1} arises corresponding to the C=N group.

As in the case of most 1,5-diketones studied previously, it was not possible to isolate pure products of the reaction of diketones Ia and Ib with ammonia but such a product was identified in the case of diketone Ib by the addition of two moles of HCN with the formation of dicyanide II. The IR spectrum of II does not show bands for the C=O and C=C groups but has a band at 2240 cm^{-1} corresponding to C≡N.

The reaction of diketone Ib with primary amines such as methyl p-aminobenzoate and benzidine proceeds slowly. The reaction products are derivatives of 2-tert-butyl-1,4,5,6,7,8-hexahydroquinoline III and IV. The IR spectra of these compounds have C=C bands in the vicinity of 1690 and 1660 cm^{-1}. The spectrum of III also has a strong band at 1720 cm^{-1} corresponding to the CO_2CH_3 group. The PMR spectrum of IV has signals for the vinyl protons

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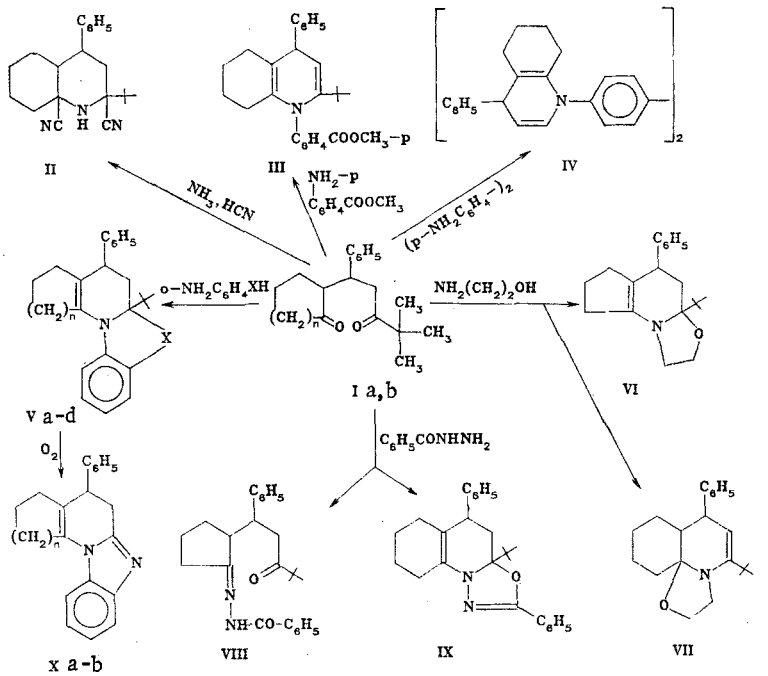
at 5.1 ppm (2H, d, J = 6 Hz) and benzylic protons which are coupled to the vinyl protons at 3.9 ppm (2H, d, J = 6 Hz), as well as a singlet for the tert-butyl group at 0.9 ppm (18H). Diketone Ia reacts with benzidine extremely slowly.



I, X a n=1, b n=2; V a n=1, X=O, b n=2, X=O; c n=1, X=NH; d n=2, X=NH

The reaction of diketones Ia and Ib with primary amines containing an additional nucleophilic site at the β-position relative to the amino group such as o-phenylenediamine, o-aminophenol, ethanolamine, and benzoylhydrazine proceeds more readily but still more slowly than for other diketones [3], apparently, as a consequence of steric hindrance. In most cases, oxa- or azaindolizine species (V-VII, IX) are formed. However, the course of the reaction depends both on the ring size in the alicyclic fragment of the diketone (VI-VII, VIII-IX) and the nature of the nucleophile (V-VII). The predominant variant involves closure of the azoline ring toward the pivaloyl fragment of the diketone to give derivatives of 1,2-azolino- and 1,2-azolidinooctahydroquinolines or their hexahydropyridine analogs containing an angular tert-butyl group (V, VI, and IX). The steric interactions between the tert-butyl group and the phenyl ring of the reagent likely hinder an alternative course in the reaction of diketones Ia and Ib with o-aminophenol and o-phenylenediamine, while the reaction of diketone Ia with ethanolamine is hindered by strain in the heteroanalog of spiro-[4,4]nonane formed. Such strain is less in the reaction of diketone Ib with ethanolamine, which leads to closure of the azolidine ring toward the cyclohexanone fragment of the diketone (VII). The tendency for "double cyclization" is less with benzoylhydrazine than with other bifunctional amines [3]. Hence, the oxadiazoline ring is closed only in the case of diketone Ib (IX), while monohydrazone VIII is found in the case of diketone Ia.

The formation of V, VI, and IX excludes the initial reaction of one carbonyl group of the diketone with both nucleophilic sites of the reagent. (Such a scheme was proposed for the reaction of 1,4-diketones with 2-amino-1,3-diols [6].) The realization of such a scheme would indicate that the pivaloyl carbonyl reacts prior to the cyclohexanone carbonyl, which is quite unlikely. Apparently, a derivative of 1,4-dihydropyridine is found in the case with subsequent intramolecular nucleophilic addition. The possibility of such an addition was demonstrated by Eremeeva et al. [3].

The IR spectra of V-VII and IX have one band for the C=C group in the vicinity of 1670 cm^{-1} (and not two bands as in the spectra of the III and IV). The spectra of Va, Vb, VI, and VII do not show an OH group band, while the spectrum of Vd has a single band at 3300 cm^{-1} which is characteristic for a secondary amino group. The spectrum of IX lacks bands for ketonic and amide carbonyl groups and an NH group but has a C=N band at 1630 cm^{-1}. On the other hand, the spectrum of VIII has strong bands for the pivaloyl carbonyl at 1700 cm^{-1} and amide carbonyl at 1675 cm^{-1} as well as bands at 3180 (NH) and 1650 cm^{-1} (C=N).

TABLE 1. Characteristics of Compounds Synthesized

Compound	Bp, °C	Found, %			Chemical formula	Calculated, %			Yield, %
		C	H	N		C	H	N	
Ia	70—73	79,5	8,8	—	$C_{18}H_{24}O_2$	79,4	8,8	—	84
Ib	124—126	80,3	9,4	—	$C_{19}H_{26}O_2$	80,0	9,1	—	86
II	175—176	78,7	8,3	13,0	$C_{21}H_{27}N_3$	78,5	8,4	13,1	85
III	87—88	80,8	7,9	4,0	$C_{27}H_{31}NO_2$	80,8	7,7	3,5	31
IV	210—211	87,5	8,1	4,2	$C_{50}H_{56}N_2$	87,7	8,2	4,1	56
Va	81—83	83,0	7,8	4,4	$C_{24}H_{27}NO$	83,5	7,8	4,1	38
Vb	94—95	83,0	8,2	3,9	$C_{25}H_{29}NO$	83,3	8,0	3,9	69
Vd	89—90	83,4	8,5	7,8	$C_{25}H_{30}N_2$	83,8	8,4	7,8	48
VI	oil	81,1	9,3	4,4	$C_{20}H_{27}NO$	80,8	9,1	4,7	19
VII	80—81	81,1	9,4	4,7	$C_{21}H_{29}NO$	81,0	9,3	4,5	49
VIII	125—125[a]	77,1	7,4	7,1	$C_{25}H_{30}N_2O_2$	76,9	7,7	7,2	36
IX	141—143	80,5	7,8	7,0	$C_{26}H_{32}N_2O$	80,8	7,8	7,2	46
Xa[b]	221—223[c]	73,8	6,1	8,9	$C_{20}H_{19}ClN_2$	74,3	5,9	8,7	32
Xb	105[d]	82,9	8,2	9,4	$C_{21}H_{20}N_2$	83,3	8,3	9,3	30

[a]From petroleum ether. [b]Hydrochloric salt. [c]From dioxane. [d]With decomposition. The remaining compounds were recrystallized from ethanol.

The PMR spectra of V, VI, and IX lack signals for vinyl protons, while the spectrum of VII has a vinyl proton signal as a doublet at 4.8 ppm (J = 3 Hz). The benzyl proton coupled to this vinyl proton gives a quartet at 3.3 ppm (J_1 = 9, J_2 = 3 Hz). The value of the first coupling constant indicates cis-axial orientation of the benzyl proton and the coupled angular proton.

Loss of the angular tert-butyl group and hydrogen from nitrogen occurs in Vc and Vd even at room temperature with the formation of Xa and Xb which contain the 1-vinylbenzimidazole fragment [4]. Thus, Vc could not be isolated and product Xa is obtained directly instead (as the hydrochloride salt); Vd may be stored only in a sealed ampul. In contrast to the cleavage of hydrocarbons from 2,2-dialkylbenzimidazolines, for which a carbanion mechanism has been proposed [7], the present transformation is free radical in nature [4] and proceeds by the action of oxygen. Initial attack of oxygen likely occurs at the N—H bond and the radical formed fragments with the loss of a tert-butyl radical, which is then transformed into tert-butyl hydroperoxide (at the end of the conversion, the reaction mixture gives a strong test for peroxide).

The structures of Xa and Xb were supported by their UV spectra [4]. The IR spectrum of Xb has a band at 1550 cm^{-1} which is characteristic for benzimidazoles substituted within the heterocycle [8] and does not have an NH band. The PMR spectra of Xb and the hydrochloride salt of Xa do not have the characteristic tert-butyl singlet.

In contrast to Vc and Vd, compounds Va, Vb, and IX are entirely stable upon storage. Gradual decomposition of VI occurs upon storage to give diketone Ia and ethanolamine (apparently, due to hydrolysis).

EXPERIMENTAL

The IR spectra were taken on a Specord IR-75 spectrometer in vaseline oil and chloroform. The PMR spectra were taken on a Bruker HX-90E spectrometer with TMS internal standard. The mass spectra were taken on an MKh-1303 mass spectrometer with 30 eV ionization energy. The course of the reactions and the purity of the products were monitored using thin-layer chromatography on Silufol plates. The characteristics of the compounds synthesized are given in Table 1.

4,4-Dimethyl-1-phenyl-1-(2'-oxocycloalkyl)-3-pentanones (Ia and Ib). A sample of 18 ml 40% NaOH was added to a solution of 0.1 mole benzalpinacoline and 0.3 mole cycloalkanone in 300 ml ethanol. The mixture was maintained for 24 h at room temperature. In the case of cyclopentanone, the mixture was then diluted with 600 ml water and extracted with three 100-ml portions of ether. The ethereal extract was washed with two 50-ml portions of 5% HCl and then water. The ether was evaporated and the residue was distilled in vacuum. The fraction with bp 183-188°C (3 mm) was collected. Diketone Ia was crystallized in the receiver. In the case of cyclohexanone, the precipitate of diketone Ib was filtered off and the filtrate was

diluted with an additional amount of diketone. The monooximes were obtained by the reaction of diketones Ia and Ib with excess $NH_2OH \cdot HCl$–Na_2CO_3 in acetic acid.

2-tert-Butyl-4-phenyl-2,8a-dicyanoperhydroquinoline (II). A suspension of 0.5 g diketone Ib in 10 ml ethanol was saturated with ammonia and the homogeneous solution formed was maintained for 18 h at room temperature. Then, this solution was added dropwise with cooling and stirring to a solution of 1 g KCN in 10 ml 80% acetic acid. Dicyanide II was filtered off after 2 h.

Reaction of Diketones Ia and Ib with Compounds with a Primary Amino Group. A sample of about 30 mg p-toluenesulfonic acid was added to a solution of 2 g diketone and the corresponding amount of the amino component in 30-40 ml xylene (or, in the case of VII, benzene) and heated at reflux with a Dean-Stark trap until water was no longer separated (usually 4-8 h, but 17 h in the case of diketone Ia with o-phenylenediamine). The diketone-amine molar ratios were 2.1:1, 1.1:1, and 1:2 for the preparation of IV, Xa, and both VII and VIII, respectively. This molar ratio was 1:1.1 for the remaining cases. Upon termination of the heating, the solvent was distilled off at reduced pressure. Then, in the syntheses of III-Vb, Vd, VII, and IX, the residue is poured into 10 ml ethanol, while in the preparation of VIII, the residue is poured into 10 ml 10:1 ether–hexane. After 24 h (72 h in the case of Vb), the reaction product is filtered off. In the case of Va and VI, the residue was subjected to chromatography on alumina with grade II activity after distillation of the xylene; Va was eluted with 30:1 hexane–ether and VI was eluted with 40:1 hexane–ether. In the case of the reaction of Ia with o-phenylenediamine, the residue after distilling off the xylene was poured into ethanol and maintained for seven days. Then, the ethanol was evaporated and the residue was subjected to chromatography on alumina with grade II activity with the elution of Xa by ether. The ethereal eluate was saturated with HCl gas and the hydrochloride salt of Xa was filtered off.

Conversion of Vd to Xb. A. A thin-layer chromatography spot for Xb appeared after letting a crystalline sample of Vd stand in the air for 24 h. Thin-layer chromatography indicated the presence of Vd as an impurity in Xb upon standing for seven days.

B. In the case of a 5% solution of Vd in ethanol, dioxane, and benzene, the conversion is complete after 7-10 days as indicated by thin-layer chromatography.

C. Thin-layer chromatography indicates complete conversion of a 5% ethanol solution of Vd upon irradiation with a PRK-4 mercury-quartz lamp. The same result is obtained upon the addition of a few drops of aqueous $FeCl_2$ to a solution of Vd in ethanol. Evaporation of the solutions after running the reactions according to procedures B and C yielded Xb.

LITERATURE CITED

1. M. N. Tilichenko and N. N. Minaeva, Zh. Org. Khim., 19, 2516 (1983).
2. V. A. Kaminskii, I. V. Stepanchenko, and M. N. Tilichenko, Khim. Geterotsikl. Soedin., No. 9, 1251 (1979).
3. L. M. Eremeeva, T. V. Moskovkina, Yu. V. Vasilenko, A. N. Saverchenko, V. A. Kaminskii, and M. N. Tilichenko, Khim. Geterotsikl. Soedin., No. 2, 240 (1979).
4. V. A. Kaminskii, T. V. Zabolotnova, T. V. Novikova, and M. N. Tilichenko, Zh. Org. Khim., 17, 670 (1981).
5. G. Ferard, R. Ropert, M. Keravec, and P. F. Casals, Compt. Rend., C, 279, 957 (1974).
6. H. S. Broadbent, W. S. Burnham, R. M. Sheeley, and R. K. Olsen, J. Heterocycl. Chem., 13, 337 (1976).
7. R. C. Elderfield and R. L. McClanahan, J. Am. Chem. Soc., 82, 1982 (1960).
8. K. J. Morgan, J. Chem. Soc., 2343 (1961).